

12 **EUROPEAN PATENT APPLICATION**

21 Application number: 86111429.6

22 Date of filing: 19.08.86

51 Int. Cl.: **C 07 C 57/38, C 07 C 51/00,**
C 07 D 233/00, C 07 D 277/34,
C 07 D 277/36, C 07 D 263/42

30 Priority: 23.08.85 JP 184084/85
23.08.85 JP 184085/85

43 Date of publication of application: 04.03.87
Bulletin 87/10

84 Designated Contracting States: AT BE CH DE FR GB IT LI
LU NL

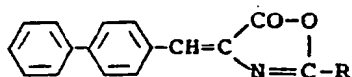
71 Applicant: **LEDERLE (JAPAN) LTD.**, Hattori Bldg., 5th
Floor 10-3 Kyobashi 1-chome, Chuo-ku Tokyo (JP)

72 Inventor: **Shimada, Osamu**, 26-41, Hanezawa 1-chome,
Fujimi-shi Saitama-ken (JP)
Inventor: **Aoyagi, Sakae**, 3-6-1004, Tate 2-chome,
Shiki-shi Saitama-ken (JP)
Inventor: **Nagase, Yunosuke**, 2-7, Nishi-Oizumi 3-chome,
Nerima-ku Tokyo (JP)

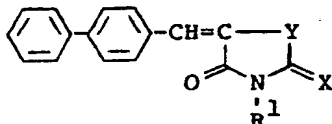
74 Representative: **Kraus, Walter, Dr. et al**, Patentanwälte
Kraus, Welsert & Partner Thomas-Wimmer-Ring 15,
D-8000 München 22 (DE)

54 Process for producing 4-biphenylacetic acid.

57 Novel and improved simple process for producing 4-biphenylacetic acid or its salt useful as an antiinflammatory and analgesic agent. The process starts from 4-biphenylaldehyde and goes through a compound of the formula



or



wherein R represents a substituted or unsubstituted phenyl or lower alkyl group, R¹ represents a hydrogen atom, a lower alkyl group or a carboxy-lower alkyl group, X represents an oxygen or sulfur atom and Y represents a sulfur atom or NH-

BEST AVAILABLE COPY

- 1 -

BACKGROUND OF THE INVENTION

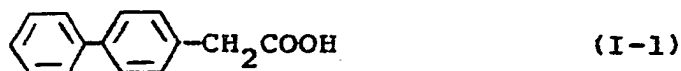
1. Field of the Invention

This invention relates to a process for producing 4-biphenylacetic acid or its salt, and more specifically, to a simple process for producing 4-biphenylacetic acid or its salt using 4-biphenylaldehyde as a starting material.

2. Description of the Prior Art

4-Biphenylacetic acid represented by the following formula I-1 is a known compound having excellent anti-inflammatory, analgesic and antipyretic activities. A sodium salt and alkyl esters of this compound are now being widely tested as anti-inflammatory and analgesic agents for humans.

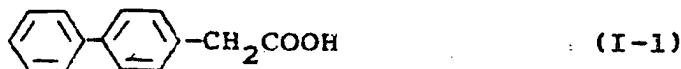
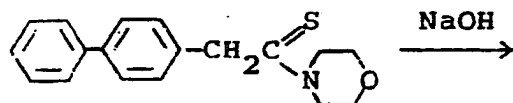
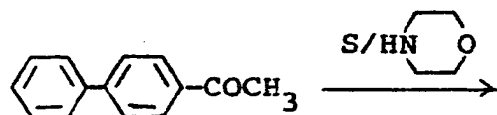
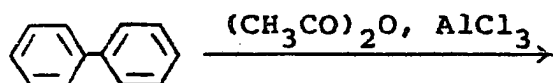
15



The following processes have previously been known typically for the production of 4-biphenylacetic acid of formula I-1.

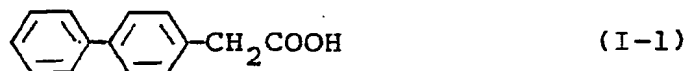
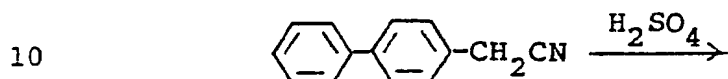
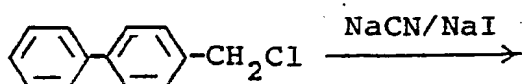
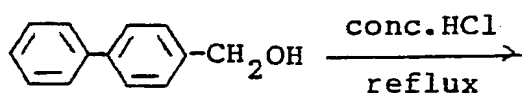
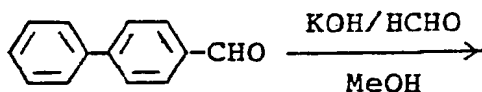
Process A

20

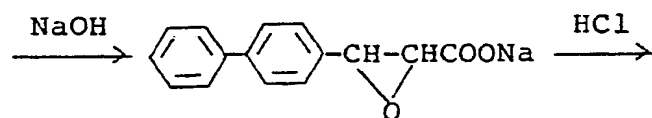
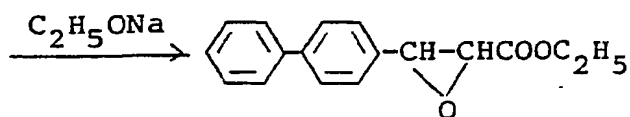
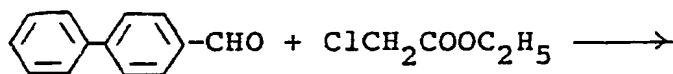


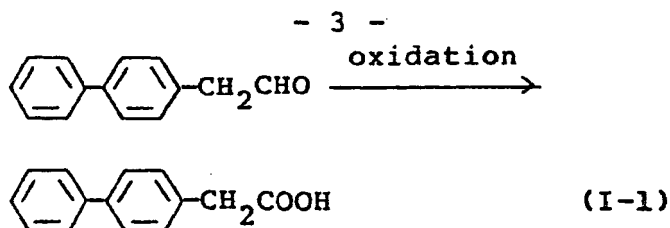
- 2 -

A process for producing 4-biphenylacetic acid which comprises converting biphenyl into 4-biphenylacetyl by the Friedel-Crafts reaction with acetic anhydride-aluminum chloride, and then subjecting 4-biphenylacetyl to the Willgerodt reaction.

Process B

A process for producing 4-biphenylacetic acid, which comprises using 4-biphenylaldehyde as a starting material and subjecting it to a series of steps of reduction, chlorination, nitrilation and hydrolysis.

Process C



A process for producing 4-biphenylacetic acid, which comprises reacting 4-biphenylaldehyde with
 5 ethyl chloroacetate to form 4-biphenylpropionaldehyde in which the side chain is elongated by one carbon atom, and then oxidizing the resulting compound.

According to process A, biphenyl as a starting material is available at a low cost, but long periods of
 10 time are required to perform treating operations in the steps necessary for the production of 4-biphenylacetic acid. Furthermore, since the process goes through a sulfur compound as an intermediate, offensive odors are released and large quantities of by-products occur.
 15 Hence, a complex purifying operation is required to produce the desired 4-biphenylacetic acid in a good purity. The yield of the final product, too, is not so good. In addition, process A has the industrial disadvantage that the entire steps cannot be performed in a
 20 single reactor (one-pot).

Process B has a number of process steps and therefore results in a decrease in yield. Furthermore, as is the case with process A, a one-pot operation cannot be employed. Moreover, since very poisonous sodium
 25 cyanide is used, process B cannot virtually be applied to industrial production of 4-biphenylacetic acid.

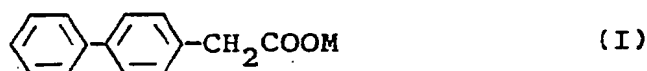
According to process C, the treatment operations can be easily carried out since the reaction conditions are not so severe. But it has a number of
 30 steps, and the yield of the product in condensation between 4-biphenylaldehyde and ethyl chloroacetate is not so high. In addition, large amounts of by-products occur, and a complex purifying step is necessary.

- 4 -

With the above background, the present inventors have extensively made investigations in order to establish a simple industrial process for producing 4-biphenylacetic acid in good yields. These investigations have led to the discovery that 4-biphenylacetic acid can be easily produced in good yields under mild conditions by using 4-biphenylaldehyde as a starting material, reacting it with an N-acylglycine or lactam compound to form azlactone-like compound, converting the resulting compound into alpha-keto acid, etc., and decarboxylating or heat-treating alpha-keto acid, etc.; and that since the entire steps of this process can be carried out in a single reactor (one-pot), this process is suitable for the industrial production of 4-biphenylacetic acid.

15 SUMMARY OF THE INVENTION

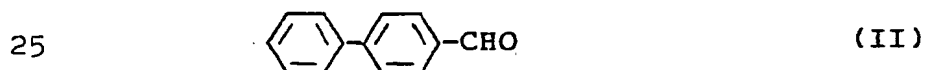
The present invention provides a process for producing 4-biphenylacetic acid or its salt represented by the following formula I



20 wherein M represents an alkali metal or a hydrogen atom,

which comprises either

(a) reacting 4-biphenylaldehyde represented by the following formula II



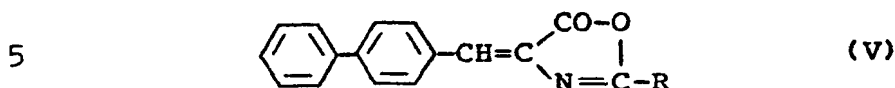
25 with an N-acylglycine represented by the following formula III



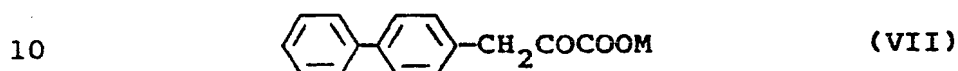
wherein R represents a substituted or unsub-

- 5 -

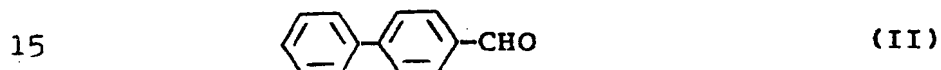
stituted phenyl or lower alkyl group,
in the presence of a base to convert 4-biphenylaldehyde
into an azlactone compound represented by the following
formula V



wherein R is as defined above,
heating the resulting azlactone compound of formula V,
and if desired, neutralizing it to form an alpha-keto
acid represented by the following formula VII



wherein M is as defined above,
and thereafter decarboxylating the alpha-keto acid; or
(b) reacting 4-biphenylaldehyde of the follow-
ing formula II

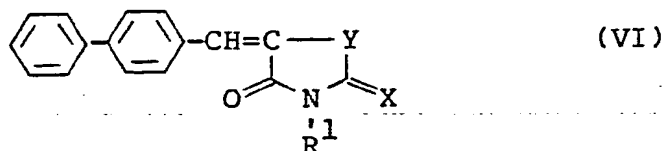


with a lactam compound represented by the following
formula IV

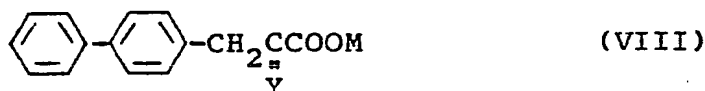


20 wherein R¹ represents a hydrogen atom, a
lower alkyl group or a carboxy-lower alkyl
group, X represents an oxygen or sulfur atom,
and Y represents a sulfur atom or -NH-,
in the presence of a base to form a condensate repre-
sented by the following formula VI

- 6 -

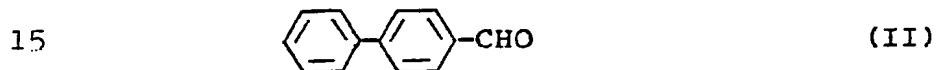


wherein R^1 , X and Y are as defined above,
 heating the resulting condensate of formula VI in the
 presence of an alkali base, and if desired, neutralizing
 5 it to form a derivative represented by the following
 formula VIII



wherein M and Y are as defined above,
 and treating the derivative of formula VIII with a per-
 10 oxide in the presence of an aqueous base.

More specifically, as a first variant, the
 present invention provides as a first variant a process
 which comprises reacting 4-biphenylaldehyde of the
 following formula II

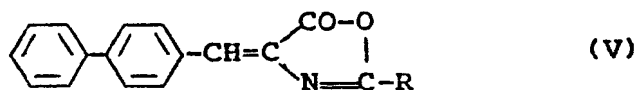


with an N-acylglycine represented by the following formula
 III



wherein R represents an unsubstituted or sub-
 20 stituted phenyl or lower alkyl group,
 in the presence of a base to convert 4-biphenylaldehyde
 into an azlactone compound represented by the following
 formula V

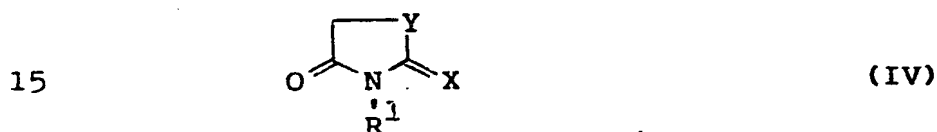
- 7 -



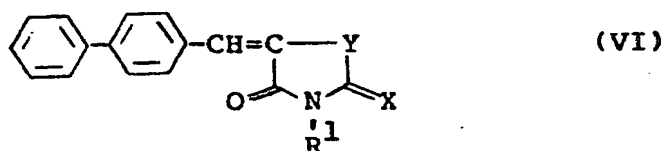
wherein R is as defined above,
 heating the resulting azlactone compound of formula V in
 the presence of an alkali metal base and if desired,
 5 neutralizing it to form an alpha-keto acid represented by
 the following formula VII



wherein M represents an alkali metal or a
 hydrogen tom,
 10 and thereafter decarboxylating the alpha-keto acid.
 As a second variant, the present invention
 provides a process which comprises reacting 4-biphenyl-
 aldehyde of formula II with a lactam compound represented
 by the following formula IV



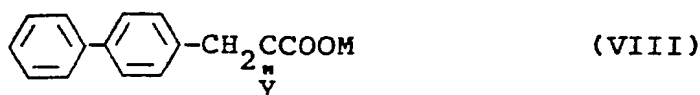
wherein R¹ represents a hydrogen atom, a
 lower alkyl group or a carboxy-lower alkyl
 group, X represents an oxygen or sulfur atom,
 and Y represents a sulfur atom or -NH-,
 20 in the presence of a base to form a condensate repre-
 sented by the following formula VI



- 8 -

wherein R^1 , X and Y are as defined above, heating the condensate of formula VI in the presence of an alkali base and if desired, neutralizing it to form a derivative represented by the following formula VIII

5



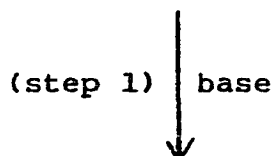
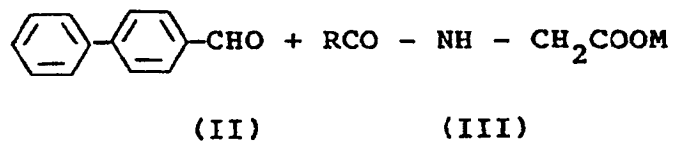
wherein Y is as defined above, and M represents an alkali metal or a hydrogen atom, and thereafter treating the resulting derivative in an aqueous solvent.

10 The process variants of this invention can be carried out as a one-pot process by which all the steps are carried out in the same reactor without isolating the compound of formula V or VI resulting from reaction of 4-biphenylaldehyde with the compound of formula III or
 15 IV and the compound of formula VII or VIII subsequently obtained. According to a particularly preferred embodiment, the process of this invention can be carried out by heat-treating 4-biphenylaldehyde of formula II and the compound of formula III or IV in the presence of a base
 20 and subsequently decarboxylating the product or treating it with a peroxide in the presence of an aqueous base in the same reactor. This embodiment is particularly preferred as an industrial simple process.

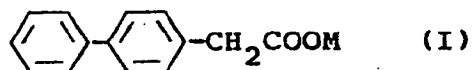
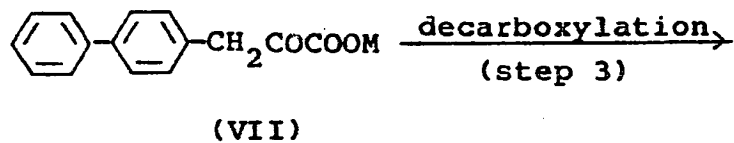
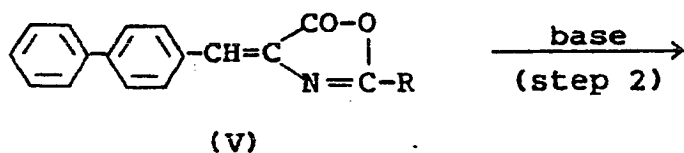
DETAILED DESCRIPTION OF THE INVENTION

25 In the process of this invention, 4-biphenylaldehyde of formula II and the compound of formula III or IV are used as starting materials. The process is schematically shown below by chemical formulae.

- 9 -

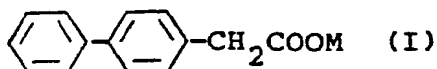
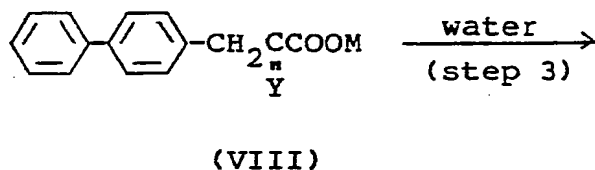
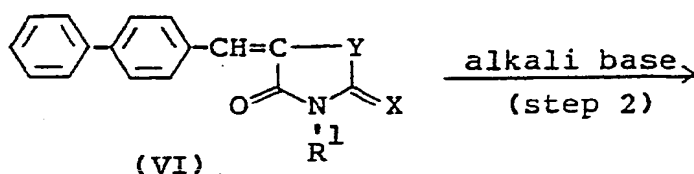
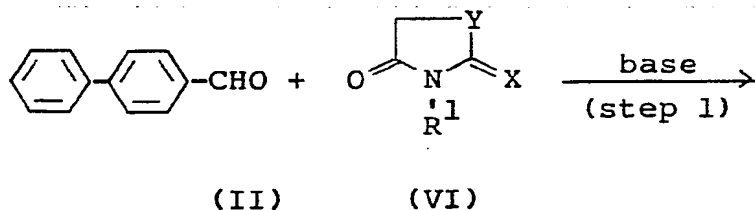
First process variant

5



10 (In the above chemical formulae, R and M are as defined hereinabove.)

- 10 -

Second process variant

(In the above chemical formulae, R^1 , X, Y and
 10 M are as defined hereinabove.)

In the process of this invention, steps 1, 2
 and 3 in each of the above process variants may be carried
 out individually, or in the same reactor as a one-pot
 process.

15 The term "lower", used throughout the present
 specification and claims to qualify a group or a com-
 pound, means that the group or compound so qualified
 contains not more than 6, preferably not more than 4,
 carbon atoms.

20 The "lower alkyl group", as used in the present
 specification and claims, denotes a linear or branched

- 11 -

alkyl group having 1 to 6 carbon atoms. Examples include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, neopentyl and n-hexyl groups.

5 The substituent R in the N-acylglycine represented by formula III is an unsubstituted or substituted phenyl or lower alkyl group. Examples include a phenyl group; a phenyl group substituted by 1 to 3, preferably 1 or 2, substituents selected from lower alkyl groups,
10 lower alkoxy groups and halogen atoms, such as p-tolyl, 4-chlorophenyl, 4-methoxyphenyl and 3,4-dimethoxyphenyl groups; and linear or branched alkyl groups having 1 to 6 carbon atoms such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, t-butyl, n-pentyl, iso-pentyl, neo-
15 pentyl and n-hexyl groups.

 The "carboxy-lower alkyl group" is a lower alkyl group substituted by the carboxyl group, such as carboxymethyl, alpha-carboxyethyl, alpha-carboxypropyl and beta-carboxyethyl groups. Those having the carboxyl
20 group at the alpha-position are preferred.

 Specific examples of the N-acylglycine of formula III used in the first process variant are N-benzoylglycine, N-(p-toluoyl)glycine, N-anisoylglycine, N-acetylglycine, N-propionylglycine and N-(n-butyryl)
25 glycine. Of these, N-benzoylglycine is preferred because it is easily available at a low cost.

 Examples of the lactam compound of formula IV used in the second process variant typically include 2-thioxo-4-thiazolidinone (rhodanine), N-methyl-2-thioxo-
30 4-thiazolidinone, 2,4-imidazolidinone (hydantoin) and N-carboxymethyl-2-thioxo-4-thiazolidinone.

 The first and second process variants in accordance with this invention will be described in more detail with reference to the individual steps schematically
35 shown above. (In the case of the one-pot processes, the conditions of steps 1 to 3 may be properly combined and

- 12 -

the process can be performed in a single reactor. This will also be described hereinafter.)

Step 1

In this step, 4-biphenylaldehyde of formula
5 II is reacted with the N-acylglycine of formula III or the lactam compound of formula IV in the presence of a base to form the azlactone compound of formula V or the condensate of formula VI.

The reaction is carried out in the presence of
10 a base with or without a solvent. Examples of the base that can be used in this reaction are ammonia; organic tertiary amines such as trimethylamine, triethylamine, benzyldimethylamine, benzyldiethylamine, N-methylmorpholine, N-ethylpiperidine and N,N-diisopropylethylamine;
15 aromatic amines such as pyridine and 2-pyrroline; metal salts of organic acids such as sodium formate, sodium acetate and potassium acetate; and inorganic bases, for example carbonates and bicarbonates of alkali metals and alkaline earth metals such as lithium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate,
20 lithium carbonate, calcium carbonate and barium carbonate. Of these, sodium acetate, potassium acetate, and triethylamine are preferred. Sodium acetate is especially preferred. Since 4-biphenylaldehyde of formula II is a
25 liquid and has a low boiling point, it can concurrently serve as a solvent and therefore, the reaction may be carried out in the absence of solvent. Alternatively, the reaction may be carried out in the presence of a solvent which does not directly participate in the re-
30 action.

Specific examples of such a solvent include polar aprotic solvents such as acetonitrile, dimethylformamide, dimethylacetamide and dimethyl sulfoxide; ethers such as tetrahydrofuran and dioxane; inert alkyl
35 halides such as dichloromethane and chloroform; aromatic solvents such as benzene, toluene, xylene, chlorobenzene,

- 13 -

dichlorobenzene and nitrobenzene; and organic acids and organic acid anhydrides such as acetic acid and acetic anhydride. Of these, toluene, chlorobenzene and dioxane are preferred.

5 In this step, it is convenient to perform the reaction using generally 1 to 3 moles, preferably 1 to 1.5 moles of the N-acylglycine of formula III or the lactam compound of formula IV per mole of 4-biphenylaldehyde of formula II in the presence of generally 1 to 10 moles, preferably 1 to 2 moles, of the base and about 1 to 10 moles, preferably 2 to 5 moles, of acetic anhydride.

15 The reaction temperature and time are not restricted in a generally manner because they vary depending upon the type of the base used and the presence or absence of the solvent. Generally, in the absence of solvent, the temperature is about 0 to 150°C, preferably about 50 to about 100°C, and the time is about 0.1 to about 5 hours, preferably about 0.5 to about 1.5 hours.

20 In the case of using a solvent, the reaction is suitably carried out at a temperature near the boiling point of the used solvent for about 0.1 to about 12 hours, preferably about 0.5 to about 5 hours.

In the first step, the azlactone compound of formula V or the condensate of formula VI can be obtained mainly as crystals in a yield of about 90% or in a quantitative yield. This compound may be used in the next step 2 without purification.

Step 2

30 In this step, the azlactone of formula V or the condensate of formula VI obtained in step 1 is heated in the presence of a base to convert it into the compound of formula VII or VIII.

35 Examples of the base used in this step are hydroxides of alkali metals or alkaline earth metals such as sodium hydroxide, potassium hydroxide, lithium

- 14 -

hydroxide, calcium hydroxide and magnesium hydroxide, and the same carbonates or bicarbonates of such metals as described with regard to step 1. The amount of the base can generally be 1 to 5 moles, preferably 1 to 2 moles, per mole of the compound of formula V or VI.

In this reaction, the compound of formula V or IV and the base are heated usually in the presence of a solvent. The solvent used at this time may, for example, be water alone or a mixture of water with any of the various organic solvents illustrated above with regard to step 1.

The heating temperature is generally about 50 to about 150°C, preferably about 100 to about 120°C. When the aforesaid mixture of water and an organic solvent is used, the heating may conveniently be carried out at a temperature near the boiling point of the organic solvent. At the above temperature, the reaction comes to completion usually in about 0.5 to about 15 hours, preferably about 1 to about 10 hours. As a result, the desired compound of formula VII or VIII can be obtained in a nearly quantitative yield.

In this case, the compound of formula VII or VIII is obtained in the form of a salt corresponding to the base used. When, for example, sodium hydroxide is used as the base, the compound is obtained as a sodium salt (M=Na). The salt of the compound may be converted to a free compound (M=H) by neutralizing it with an acid in a customary manner.

Step 3

In this step, the alpha-keto acid of formula VII obtained in step 2 is decarboxylated or the compound of formula VIII is treated with a peroxide in an aqueous base, thereby to obtain 4-biphenylacetic acid of formula I. This step can be carried out by methods known per se. Decarboxylation of the compound of formula VII and treatment of the compound of formula VIII are carried out in

- 15 -

the same manner. For example, it is carried out by treating the compound of formula VII or VIII with an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide and a peroxide such as hydrogen peroxide
5 in the presence of a suitable amount of water.

The above reaction can be carried out by treating the compound of formula VII or VIII with usually 1 to 10 moles, preferably 1 to 3 moles, per mole of the compound of formula VII or VIII, of an alkali metal hydroxide
10 such as sodium hydroxide and generally 1 to 10 moles, preferably 1 to 5 moles, per mole of the compound of formula VII or VIII, of a peroxide such as hydrogen peroxide at a temperature in the range of about 0 to about 100°C, preferably about 10 to about 40°C, for a period of
15 about 1 to about 20 hours, preferably about 5 to about 10 hours. As a result, the desired 4-biphenylacetic acid or its salt represented by formula I can be obtained in good yields.

When in this step 4-biphenylacetic acid of
20 formula I is obtained in the form of a salt such as a sodium salt, it may as required be neutralized to convert it to a free acid, and the desired 4-biphenylacetic acid may be obtained in pure form by applying known isolating and purifying means such as extraction, chromatography
25 and recrystallization to the free acid.

As stated above, in steps 1, 2 and 3 in accordance with this invention, the final products in these steps can be obtained in good yields by a simple means such as heating. The present invention is particularly
30 characterized in that these steps 1, 2 and 3 can be carried out in a single reactor (one-pot process). This one-pot process will be described in detail below.

One-pot process

The one-pot process may be carried out by properly selecting those conditions which can be practiced
35 in a single reactor from the conditions in steps 1, 2 and

- 16 -

3 described hereinabove. Specifically, it is preferably carried out as follows:- In the following, the one-pot process will be described with regard to the first process variant, but the second process variant may also be
5 carried out by a one-pot technique in the same way.

In the first step, 1 mole of 4-biphenylaldehyde represented by formula II is reacted with 1 to 3 moles, preferably 1 to 1.5 moles, of the N-acylglycine of formula III in the presence of sodium acetate, for example, as a base in the absence of a solvent or in a
10 solvent such as toluene. In this case, sodium acetate and toluene as the base and solvent are selected because they can be directly used in the conversion reaction to the alpha-keto acid in the second step.

15 Thereafter, as the second step, the reaction mixture in the first step is directly heated to a temperature in the range of about 80 to about 150°C at the end of the treatment in the first step. Alternatively, the solvent is evaporated, and if desired, a base for
20 example a sodium hydroxide solution is further added, and the resulting mixture is heated to a temperature in the aforesaid range.

In the treatment of the second step, the azlactone compound of formula V formed in the reaction
25 system by the treatment of the first step is converted to the alpha-keto acid of formula VII quantitatively.

Thereafter, as the third step, a desired amount of a peroxide, for example, about 2 to 10 moles, per 4-biphenylaldehyde used in the first step, of hydrogen
30 peroxide is added to the reaction mixture as obtained in the second step, and the mixture was stirred at a temperature of about 10 to about 40°C for about 5 to about 10 hours.

In the third step, the alpha-keto acid of
35 formula VII is converted to 4-biphenylacetic acid or its salt of formula I which is the final product of this

- 17 -

invention.

After the treatments in the first to third steps have been carried out in the same reactor, the contents are optionally neutralized, and then subjected to a suitable combination of extraction, distillation and recrystallization to give 4-biphenylacetic acid as a pure product.

The yield of the final product in the one-pot process is as high as 70 to 80% based on the phenylaldehyde used in the first step.

Hence, the process of this invention is simpler in operation and higher in yield than the conventional processes A to C described above, and is especially advantageous for industrial production.

The steps of the process of this invention is relatively small, and the treatments in the individual steps are, for example, heating and stirring which are simple. Moreover, the reaction conditions are not severe. Accordingly, the productivity of the process of this invention is very good as an industrial process.

EXAMPLES

The following Examples illustrate the process of this invention both in a stepwise mode and in a one-pot mode. It should be understood, however, that the invention is never limited to these examples alone.

Example 1

To a solution of 4-biphenylaldehyde (5g, 0.027 mol) in acetic anhydride (8 ml) were added N-benzoylglycine (5.47g, 0.034 mol) and sodium acetate (2.3g). The mixture was stirred at 40-50°C for 2 hours, then poured into hot ethanol, and cooled. The precipitated crystals were collected by filtration to give 8.3g (94% yield) of 2-phenyl-4-(4'-biphenylmethylidene)-5-oxazolone as yellow crystals. Furthermore, the filtrate was concentrated to give an additional 0.4g (5% yield) of the crystals. (Total yield: 99%)

- 18 -

mp: 187-188°C

IR spectrum (KBr): 1790 cm⁻¹UV spectrum: λ_{max} 380 nm

Example 2

5 A mixture of 2-phenyl-4-(4'-biphenylylmethylidene)-5-oxazolone (3g, 9.2 mmol) prepared in Example 1 and 20% sodium hydroxide solution (15 ml) was refluxed for 2 hours. After cooling, the mixture was washed with benzene, acidified with hydrochloric acid, and extracted
10 with ethyl acetate. The combined extracts were washed with water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent in vacuo gave 2.0g (90% yield) of 4-biphenylylpyruvic acid as a crystalline solid, which was recrystallized from ethyl acetate.

15 mp: ca. 205°C (sublimed)

IR spectrum (KBr): 1660 cm⁻¹

Example 3

To 2g (8.3 mmol) of 4-biphenylylpyruvic acid prepared in Example 2 were added 0.5% sodium hydroxide
20 solution (15 ml) and 30% hydrogen peroxide (4 ml). After being stirred at 20-30°C for 4 hours, the mixture was washed with toluene, acidified with hydrochloric acid, and extracted with ethyl acetate. The combined extracts were washed with water and brine, and dried over
25 anhydrous sodium sulfate. Evaporation of the solvent in vacuo gave 1.6g (91%) of 4-biphenylylacetic acid as a crystalline solid, which was recrystallized from methyl ethyl ketone.

mp: 163-164°C

30 IR spectrum (KBr): 1688 cm⁻¹

Example 4

4-Biphenylylaldehyde (4g, 0.022 mol) was dissolved in acetic anhydride (4 ml) and N-benzoylglycine (4.33g, 0.024 mol), sodium acetate (1.84g) and toluene (28
35 ml) were added to the solution. After refluxing for 2 hours, 20% sodium hydroxide solution (65 ml) was added to

- 19 -

the reaction mixture. The mixture was refluxed for 2 hours, washed with benzene and extracted with ethyl acetate. The extract was washed with water and then with brine, dried over anhydrous sodium sulfate and concentrated in vacuo to give 5.2g (99% yield) of 4-biphenylyl-pyruvic acid as a crystalline solid.

IR spectrum (KBr): 1660 cm^{-1}

Example 5

To 3g (9.2 mmol) of 2-phenyl-4-(4'-biphenyl-methylidene-5-oxazolone obtained in Example 1 was added 15 ml of sodium hydroxide solution and the mixture was refluxed for 2 hours. After being cooled to about 10°C , 40% sodium hydroxide solution (4 ml) and 30% hydrogen peroxide were added to the solution and the mixture stirred at room temperature for 6.5 hours. The resulting solution was acidified with hydrochloric acid and extracted with benzene. The extract was washed with water and then brine, dried over anhydrous sodium sulfate and concentrated in vacuo to give 1.6g (81% yield) of 4-biphenylylacetic acid. The melting point and spectral data of the crystals obtained were identical with those of the product prepared in Example 3.

Example 6

4-Biphenylylaldehyde (5g, 0.027 mol) was dissolved in 8 ml of acetic anhydride, and N-benzoylglycine (5.47g, 0.034 mol), sodium acetate (2.3g) and toluene (35 ml) were added to the solution. The mixture was refluxed for 2.5 hours. Then 40% sodium hydroxide solution was added, and the mixture refluxed for 2 hours. After cooling, 30% hydrogen peroxide (12 ml) was added and the reaction mixture was stirred at room temperature for 5 hours. The solution was washed with cold toluene and then acidified with hydrochloric acid. The resulting crystals were collected by filtration to give 4.9g (84% yield) of 4-biphenylylacetic acid. The melting point and spectral data of the crystals obtained were identical

- 20 -

with those of the product prepared in Example 3.

Example 7

4-Biphenylylaldehyde (1kg) was dissolved in 1.5 l of acetic anhydride, and N-benzoylglycine (1.09kg), sodium acetate (0.46 kg) and toluene (5 l) were added to the solution. The mixture was refluxed for 2.5 hours. Then 40% sodium hydroxide solution was added, and the mixture refluxed for 4 hours. After cooling, 30% hydrogen peroxide was added and the reaction mixture was stirred at room temperature for 6 hours. The solution was washed with cold toluene and then acidified with hydrochloric acid. The resulting crude crystals were collected by filtration and recrystallized from methyl ethyl ketone to give 0.86kg (74% yield) of 4-biphenylylacetic acid.

Example 8

4-Biphenylylaldehyde (3g, 0.016 mol) was dissolved in acetic anhydride (4.8 ml), and 2-thioxo-4-thiazolidine (2.4g, 0.018 mol), sodium acetate (1.4g) and toluene (20 ml) were added to the solution. The mixture was refluxed for 2 hours, then extracted with ethyl acetate, washed with water, and dried. Evaporation of the solvent in vacuo gave 4.6g (94% yield) of 5-(4'-biphenylmethylenylidene)-2-thioxo-4-thiazolidinone as a yellow crystalline solid, which was recrystallized from ethyl acetate.

mp: 243-244°C

IR spectrum (KBr): 1700-1710 cm^{-1}

UV spectrum: λ_{max} 387 nm

Example 9

4-Biphenylylaldehyde (5g, 0.027 mol) was dissolved in acetic anhydride (8 ml), and N-methyl-2-thoxo-4-thiazolidinone (4.48g, 0.03 mol) and sodium acetate (2.3g) were added to the solution. The mixture was heated at 80-90°C for 2.5 hours and then cooled, and benzene and water were added. The benzene layer was separated, washed with water, and dried over anhydrous

- 21 -

sodium sulfate. The benzene solution was concentrated in vacuo to give 8.1g (quantitative yield) of N-methyl-5-(4'-biphenylylmethylidene)-2-thioxo-4-thiazolidinone as a crystalline solid, which was recrystallized from ethyl acetate.

mp: 181-182°C

IR spectrum (KBr): 1710 cm⁻¹UV spectrum: λ_{max} 387 nm

Example 10

4-Biphenylylaldehyde (3g, 0.016 mol) was dissolved in acetic anhydride (4.8 ml), and N-carboxymethyl-2-thioxo-4-thiazolidinone (3.2g, 0.017 mol) and sodium acetate (1.38g) were added to the solution. The mixture was heated at 90°C for 1 hour. Water was added, and the mixture extracted with ethyl acetate. The combined extracts were washed with water, dried over anhydrous sodium sulfate, and concentrated in vacuo to give 5.56g (95% yield) of N-carboxymethyl-5-(4'-biphenylylmethylidene)-2-thioxo-4-thiazolidinone, which was recrystallized using ethyl acetate.

mp: 256-257°C (decomposed)

IR spectrum (KBr): 1740 and 1715 cm⁻¹UV spectrum: λ_{max} 388 nm

Example 11

4-Biphenylylaldehyde (3g, 0.016 mol) was dissolved in acetic anhydride (0.5 ml), and glacial acetic acid (2.9 ml) and 2,4-imidazolidinedione (2.48g, 0.025 mol), sodium acetate (1.38g) and toluene (2 ml) were added to the solution. The mixture was refluxed for 9 hours. After cooling, water was added to the reaction mixture and the mixture extracted with benzene. The combined extracts were washed with water, dried over sodium sulfate, and concentrated in vacuo to give 4.0g (92% yield) of 5-(4'-biphenylylmethylidene)-2,4-imidazolidinedione as crystalline solid, which was recrystallized from ethyl acetate.

- 22 -

mp: 240°C (decomposed)

IR spectrum (KBr): 1778, 1718 and 1658 cm^{-1} UV spectrum: λ_{max} 333 nm

Example 12

5 To 3g (0.011 mol) of 5-(4'-biphenylmethylidene)-2,4-imidazolidinedione prepared in Example 11 was added 20% sodium hydroxide solution (10 ml) and the mixture was refluxed for 4 hours. After cooling, the reaction mixture was washed with benzene, acidified with
10 hydrochloric acid, and extracted with ethyl acetate. The combined extracts were washed with water and brine, then dried over sodium sulfate, and concentrated to give 1.3g (48% yield) of 4-biphenylpyruvic acid as a crystalline solid, which was recrystallized from ethyl acetate.

15 mp: ca. 205°C (sublimed)

IR spectrum (KBr): 1660 cm^{-1}

Example 13

To 2g (8.3 mmol) of 4-biphenylpyruvic acid prepared in Example 12 were added 0.5% sodium hydroxide
20 solution (15 ml) and 30% hydrogen peroxide (4 ml). The mixture was stirred at 25-30°C for 4 hours, then washed with toluene, acidified with hydrochloric acid, and extracted with ethyl acetate. The combined extracts were washed with water and brine, and dried over sodium
25 sulfate. Evaporation of the solvent gave 1.5g (85% yield) of 4-biphenylacetic acid as a crystalline solid, which was recrystallized from methyl ethyl ketone.

mp: 163-164°C

IR spectrum (KBr): 1688 cm^{-1}

30 Example 14

A mixture of 5-(4'-biphenylmethylidene)-2-thioxo-4-thiazolidinone (3g, 0.01 mol) prepared in Example 8 and 20% sodium hydroxide solution (25 ml) was refluxed for 2 hours, and 30% hydrogen peroxide (10 ml) at 5-10°C
35 was added to the mixture. After being stirred at room temperature for 5 hours, the solution was washed with

- 23 -

toluene, acidified with hydrochloric acid, and then extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to give 1.1g (51% yield) of 4-biphenylacetic acid as crystals. The melting point and spectral data of the crystals obtained were identical with those of the product in Example 3.

Example 15

A mixture of N-methyl-5-(4'-biphenylmethylidene)-2-thioxo-4-thiazolidinone (2g, 6.8 mmol) prepared in Example 9 and 20% sodium hydroxide solution was refluxed for 2 hours. After cooling, 30% hydrogen peroxide (5 ml) was added. The mixture was stirred at room temperature for 5 hours, washed with toluene, acidified with hydrochloric acid, and then extracted with benzene. The combined extracts were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo to give 1.1g (76% yield) of 4-biphenylacetic acid as crystals. The melting point and spectral data of the crystals were identical with those of the product in Example 3.

Example 16

4-Biphenylaldehyde (3g, 0.016 mol) was dissolved in acetic anhydride (4.8 ml) and 2-thioxo-4-thiazolidinone (2.4g, 0.018 mol), sodium acetate (1.4g) and toluene (20 ml) were added to the solution. The mixture was refluxed for 2 hours, and 40% sodium hydroxide solution was added. The mixture was refluxed for additional 2 hours. The reaction mixture was then allowed to cool, and 30% hydrogen peroxide was added. The mixture was stirred at room temperature for 5 hours, washed with toluene, acidified with hydrochloric acid, and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over sodium sulfate, and concentrated in vacuo to give 1.4g (40% yield) of 4-biphenylacetic acid. The melting point and spectral

- 24 -

data of the crystals obtained were identical with those of the product in Example 3.

Example 17

4-Biphenylylaldehyde (3g, 0.016 mol) was dissolved in acetic anhydride (0.5 ml) and glacial acetic acid (29 ml). To the solution were added sodium acetate (1.4g), 2,4-imidazolidinedione (2.48g, 0.025 mol) and toluene (2 ml), and the mixture was refluxed for 19 hours. After addition of 20% sodium hydroxide solution (16 ml), the mixture was refluxed for 2 hours. After cooling, 30% hydrogen peroxide was added to the mixture, and the whole mixture was stirred at room temperature for further 5 hours. The reaction mixture was washed with toluene, acidified with hydrochloric acid, and extracted with ethyl acetate. The combined extracts were washed with water and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a crystalline solid, which was recrystallized to give 1.5g (43% yield) of 4-biphenylylacetic acid. The melting point and spectral data of the crystals obtained were identical with those of the product in Example 3.

Example 18

A mixture of 4-biphenylylaldehyde (105g, 0.576 mol), N-benzoylglycine (114.8g, 0.641 mol), sodium acetate (48.3g), acetic anhydride (168 ml) and toluene (700 ml) was heated at an internal temperature of 80-90°C. After 4 hours, the mixture was poured into stirred cold ethanol and the resulting, yellow crystals were collected by filtration to give 166.5g (89% yield) of 2-phenyl-4-(4'-biphenylmethylidene)-5-oxazolone.

Example 19

A mixture of 2-phenyl-4-(4'-biphenylmethylidene)-5-oxazolone (150g, 0.461 mol) prepared in Example 18, potassium hydroxide (207.3g) and water (1.5 g) was refluxed with stirring for 4 hours and then cooled to 10°C. To this mixture was added 161.6 ml of 30% hydrogen

- 25 -

peroxide and the whole mixture was stirred at room temperature. After 4 hours, the reaction mixture was acidified with 10% hydrochloric acid solution. The precipitated crystals were collected by filtration and
5 recrystallized from methyl ethyl ketone to give 78.3g (80% yield) of 4-biphenylacetic acid, identical with a sample prepared in Example 3.

- 26 -

What is claimed is:

1. A process for producing 4-biphenylacetic acid or its salt represented by the following formula I



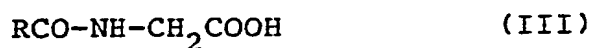
wherein M represents an alkali metal or a hydrogen atom,

which comprises either

- (a) reacting 4-biphenylaldehyde represented by the following formula II

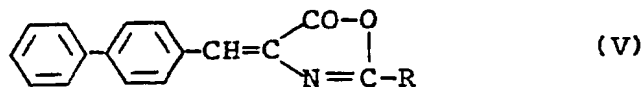


with an N-acylglycine represented by the following formula III



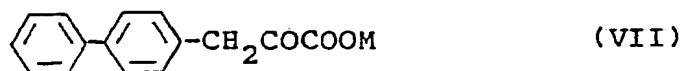
wherein R represents a substituted or unsubstituted phenyl or lower alkyl group,

in the presence of a base to convert 4-biphenylaldehyde into an azlactone compound represented by the following formula V



wherein R is as defined above,

heating the resulting azlactone compound of formula V, and if desired, neutralizing it to form an alpha-keto acid represented by the following formula VII



wherein M is as defined above,

- 27 -

and thereafter decarboxylating the alpha-keto acid; or

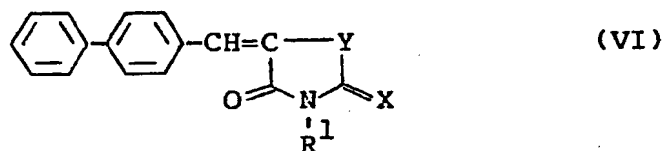
(b) reacting 4-biphenylaldehyde of the following formula II



with a lactam compound represented by the following formula IV



wherein R^1 represents a hydrogen atom, a lower alkyl group or a carboxy-lower alkyl group, X represents an oxygen or sulfur atom, and Y represents a sulfur atom or -NH-, in the presence of a base to form a condensate represented by the following formula VI.



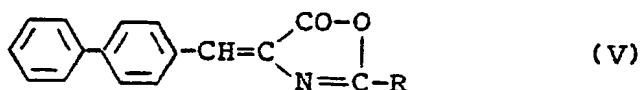
wherein R^1 , X and Y are as defined above, heating the resulting condensate of formula VI in the presence of an alkali base, and if desired, neutralizing it to form a derivative represented by the following formula VIII



- 28 -

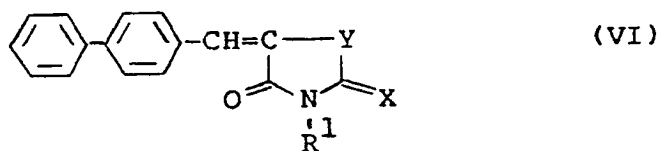
wherein M and Y are as defined above,
and treating the derivative of formula VIII with a peroxide in the presence of an aqueous base.

2. The process of claim 1 wherein the process variant (a) is carried out in a single reactor without isolating the azlactone compound of formula V and the alpha-keto compound of formula VII.
3. The process of claim 2 wherein in a single reactor, the 4-biphenylacetic acid of formula II and the N-acylglycine of formula III are heat-treated in the presence of a base, followed by decarboxylation.
4. The process of claim 1 wherein the decarboxylation is carried out by treatment with a peroxide under basic conditions.
5. An azlactone compound which is represented by the following formula V



wherein R represents an unsubstituted or substituted phenyl or lower alkyl group.

6. The process of claim 1 wherein the process variant (b) is carried out in a single reactor without isolating the condensate represented by formula VI and the derivative represented by formula VIII.
7. The process of claim 6 wherein in a single reactor, 4-biphenylaldehyde of formula III and the lactam compound of formula IV are heat-treated in the presence of a base, and then treated in an aqueous solvent.
8. A compound represented by the following formula VI



wherein R^1 represents a hydrogen atom, a lower alkyl group or a carboxy-lower alkyl group, X represents an oxygen or sulfur atom, and Y represents a sulfur atom or -NH-.

KRAUS · WEISERT & PARTNER 0 212 617

PATENTANWÄLTE
UND

ZUGELASSENE VERTRETER VOR DEM EUROPÄISCHEN PATENTAMT

Patentanwälte Thomas-Wimmer-Ring 15 D-8000 München 22

European Patent Office
Erhardtstraße 27

D-8000 Munich 2

EPA EPO-OEB
DG 1
Reçu:

11 NOV. 1986

DR. WALTER KRAUS
DIPLOMCHEMIKER

DR.-ING. ANNEKÄTE WEISERT
DIPL.-ING.

JOHANNES SPIES
DIPL.-PHYS.

THOMAS-WIMMER-RING 15
D-8000 MÜNCHEN 22
TELEFON (0 89) 22 73 77
TELEX 5-212 156 kpat d
TELEFAX (0 89) 22 79 94

UNSERE NR.:
OUR FILE:

5611 AW/eg

Bitte in der Antwort stets angeben
Please refer to in your reply

November 4, 1986

Re.: European patent application 86 111 429.6
Lederle (Japan), Ltd.

Enclosed is in triplicate a new page 28 which shall substitute page 28 as now on file.

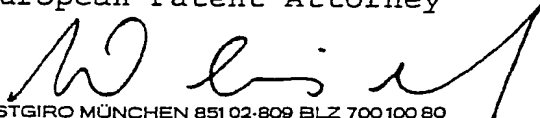
The following amendments were carried out:

1. Claim 3, line 2:
4-biphenylacetic → 4-biphenylaldehyde
2. Claim 7, line 2:
formula III → formula II.

It is politely submitted that these amendments are allowable. According to Rule 88 EPC a mistake in a document filed with the European Patent Office may be corrected on request if the request for such correction concerns claims and if the correction is obvious in the sense that it is immediately evident that nothing else would have been intended than what is offered as correction. This applies for the amendments carried out in claims 3 and 7.

Encl.
New page 28 (3fold)

European Patent Attorney



TELEGRAMMADRESSE: KRAUSPATENT POSTGIRO MÜNCHEN 851 02-809 BLZ 700 100 80
DEUTSCHE BANK MÜNCHEN 1 864 008 BLZ 700 700 10



DOCUMENTS CONSIDERED TO BE RELEVANT			EP 86111429.6
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	GB - A - 1 167 192 (BOOTS) * Example; claims *	1,6-8	C 07 C 57/38 C 07 C 51/00
	--		C 07 D 233/96
A	DE - A1 - 2 533 397 (NISSHIN) * Claims *	1,4	C 07 D 277/34 C 07 D 277/36
	--		C 07 D 263/42
A	EP - A1 - 0 037 479 (DEGUSSA) * Examples; claims *	1,8	

			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 C 57/00 C 07 D 233/00 C 07 D 277/00 C 07 D 263/00
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 18-11-1986	Examiner HOFBAUER
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

(07920) 7/11/18 3:04 PM

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)